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Note

Synthesis of new 1, 10-diethoxy-1*H*-pyrano[4, 3-*b*]quinolines and their antibacterial studies

T Dhanabal, T Suresh & P S Mohan*

Department of Chemistry, Bharathiar University, Coimbatore 641 046, India

E-mail: ps_mohan_in@yahoo.com

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A simple and one-pot synthesis of 1, 10-diethoxy-1*H*-pyrano[4, 3-*b*]quinolines **3a-e** from the respective 4-chloro-3-formyl-2-(2-hydroxyethen-1-yl)quinolines **2a-e** has been achieved (by Vilsmeier's reaction on 4-hydroxyquinaldines) by way of intramolecular cyclization when reacted with ethanol in the presence of a few drops of hydrochloric acid. All the newly synthesized compounds have been characterized by their spectral and analytical data. Anti-bacterial studies also have been carried out for some of the synthesized compounds.

Keywords: Hydroxyquinaldines, Vilsmeier Reaction, diethoxy-1*H*-pyrano[4, 3-*b*]quinolines, anti-bacterial activity

IPC: **Int.Cl.**[7] **C 07 D**

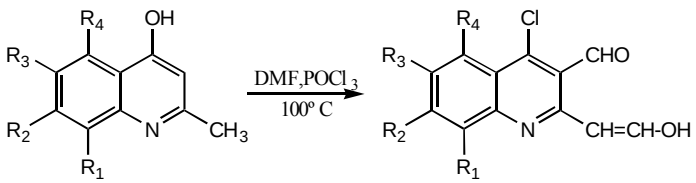
Pyranoquinolines constitute the parent ring structure of pyranoquinoline alkaloids which occur in the plant family Rutaceae. These pyranoquinoline alkaloids have gained considerable importance in recent years due to their pharmacological activities like anti-coagulant[1], coronary constricting[2], optical brightening[3] and antifungal activity[4] and their biological activities of anti-histamine, anti-allergic and mast cell stabilizer of their naturally occurring representatives. Earlier reports reveal that Vilsmeier's reagent is a mild and efficient formylating agent for reactive aromatic, heteroaromatic substrates and activating agent for activated methyl and methylene group[5-10]. Recently, we have reported the use of Vilsmeier reagent to afford newer quinoline derivatives[11].

In continuation of our work on quinoline derivatives, one of the intermediate 4-chloro-3-formyl-2-(2-hydroxyethen-1-yl)quinoline **2** was taken for deriving pyranoquinoline system *via* intra-molecular cyclization. The compound **2** reacts with ethanol in the presence of acidic condition (**Scheme I**). The nucleophilic attack of the ethoxy group on either of the formyl group or C_4 position leads to the formation of the titled compounds. It was observed that the reaction did not proceed without the addition of a few drops of conc. HCl

IR spectrum of **3a** (**Scheme II)** showed no absorption bands for formyl and hydroxyl group and appearance of bands at 1625 and 1588 cm^{-1} accounted for C=N and C=C groups respectively. In its ^1H NMR spectrum, a triplet and a quartet observed at δ 0.91 and 3.72 respectively showed the ethoxy group protons and is attached to the pyran nucleus; a triplet and a quartet at δ 1.20 and 4.20 indicates another ethoxy group protons and it is attached to the pyridine nucleus, because more deshielding is expected for ethoxy group protons at this nucleus. Two doublets were shown in the region at δ 5.61 and 6.93 and were accredited to protons at C_4 and C_3 positions respectively. A fine singlet at δ 6.10 is accounted for methine proton at C_1 position. Mass spectrum showed the molecular ion peak at m/z 271 and M+2 peak was not observed. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.65; H, 6.24; N, 5.22%.

Experimental Section

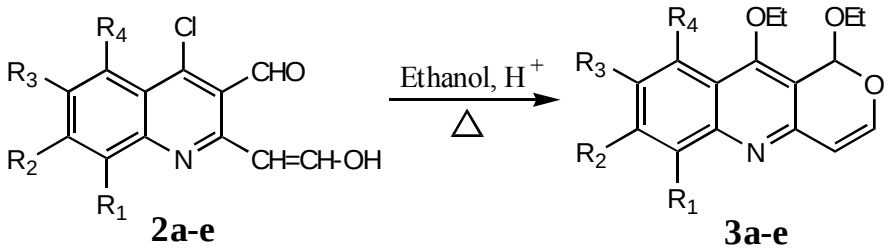
TLC was used to assess the reactions and purity of products. Melting points were determined on a



1a-e **2a-e**

a) $R_1=R_2=R_3=R_4=H$ b) $R_2=R_3=R_4=H$, $R_1=CH_3$
c) $R_1=R_2=R_4=H$, $R_3=OCH_3$ d) $R_1=R_2=R_4=H$, $R_3=Cl$
e) $R_2=R_3=H$, $R_1=R_4=CH_3$

Scheme I



2a-e **3a-e**

a) $R_1=R_2=R_3=R_4=H$ b) $R_2=R_3=R_4=H$, $R_1=CH_3$
c) $R_1=R_2=R_4=H$, $R_3=OCH_3$ d) $R_1=R_2=R_4=H$, $R_3=Cl$
e) $R_2=R_3=H$, $R_1=R_4=CH_3$

Scheme II

Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-8201 FT instrument in KBr disc and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H NMR spectra were recorded in AMX-400 MHz spectrometer in DMSO-d_6; chemical shifts are expressed in δ, ppm relative to TMS. Satisfactory elemental analyses were obtained with a Vario-EL-III C, H, N analyzer. Mass spectra were recorded on a Jeol-300 mass spectrometer at 70 eV.

Synthesis of 1, 10-diethoxy-1*H*-pyrano[43-*b*]quinoline 3a. To a solution of 4-chloro-3-formyl-2-(2-hydroxyethen-1-yl)quinoline **2a** (0.247 g) in dry ethanol (20 mL), 3-5 drops of conc. HCl were added. The mixture was kept under reflux for 4 hr. After the reaction was over, inferred through TLC, ethanol was removed by distillation and water was added to the residue. It was extracted with chloroform and dried over anhydrous sodium sulfate. The chloroform extract on silica gel column chromatography with chloroform-methanol (98:2) as eluent yielded the pyranoquinoline **3a**. Compounds **3b-e** were prepared similarly.

The intermediates **2a-e** were synthesized by the reported procedure[11].

3a: yield 78%, m.p. 290°C; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.65; H, 6.24; N, 5.22%; IR(KBr): 1625 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): 0.91(t, 3H, C_1-O-CH_2-CH_3), 1.20(t, 3H, C_{10}-O-CH_2-CH_3), 3.72(q, 2H, C_1-O-CH_2-CH_3), 4.20(q, 2H, C_{10}-O-CH_2-CH_3), 5.61(d, 1H, C_4-H, *J*=7.2Hz), 6.10(s, 1H, C_1-H), 6.93(d, 1H, C_3-H, *J*=6.9Hz), 7.50(t, 1H, C_8-H, *J*=8.0Hz,), 7.65(t, 1H, C_7-H, *J*=8.0Hz), 7.75(d, 1H, C_9-H, *J*=8.2Hz), 8.0(d, 1H, C_6-H, *J*=8.2Hz).

3b: yield 82%, m.p. 275°C; Anal Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.64; H, 6.77; N, 4.90%; IR(KBr): 1625 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): 0.92(t, 3H, C_1-OCH_2-CH_3), 1.20(t, 3H, C_{10}-O-CH_2-CH_3), 2.35(s, 3H, CH_3), 3.71(q, 2H, C_1-O-CH_2-CH_3), 4.21(q, 2H, C_{10}-O-CH_2-CH_3), 5.62(d, 1H, C_4-H, *J*=7.1Hz), 6.16(s, 1H, C_1-H), 6.92(d, 1H, C_3-H, *J*=6.9 Hz), 7.52(t, 1H, C_8-H, *J*=8.2Hz), 7.43(d, 1H, C_7-H, *J*=8.1Hz), 7.82(d, 1H, C_9-H, *J*=8.1Hz).

3c: yield 75%, m.p. 235°C; Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.43; N, 4.62%; IR (KBr): 1625 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): 0.92(t, 3H, C_1-O-CH_2-CH_3), 1.33(t, 3H, C_{10}-O-CH_2-CH_3), 3.72 (q, 2H, C_1-O-CH_2-CH_3), 3.91(s, 3H, -OCH_3), 4.32(q, 2H, C_{10}-O-CH_2-CH_3), 5.61(d, 1H, C_4-H, *J*=7.2 Hz), 6.17 (s, 1H, C_1-H), 6.98 (d, 1H, C_3-H, *J*=6.9 Hz), 7.30-7.90 (m, 3H, Ar-H).

3d: yield 60%, m.p. 210°C; Anal. Calcd for $C_{16}H_{16}NO_3Cl$: C, 62.85; H, 5.27; N, 4.58. Found: C, 62.74; H, 5.20; N, 4.67%; IR(KBr): 1625 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): 0.94(t, 3H, C_1-OCH_2-CH_3), 1.32(t, 3H, C_{10}-O-CH_2-CH_3), 3.74(q, 2H, C_1-O-CH_2-CH_3), 4.30(q, 2H, C_{10}-O-CH_2-CH_3), 5.61(d, 1H, C_4-H, *J*=7.2Hz), 6.13(s, 1H, C_1-H), 6.92(d, 1H, C_3-H, *J*=6.9Hz), 7.30-7.90(m, 3H, Ar-H).

3e: yield 75%, m.p. 215°C; Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.85; H, 6.55; N, 4.87%; IR(KBr): 1625 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): 0.92(t, 3H, C_1-O-CH_2-CH_3), 1.34(t, 3H, C_{10}-O-CH_2-CH_3), 2.32(s, 3H, C_6-CH_3), 2.41(s, 3H, C_9-CH_3), 3.76(q, 2H, C_1-O-CH_2-CH_3), 4.35(q, 2H, C_{10}-O-CH_2-CH_3), 5.64(d, 1H, C_4-H, *J*=7.2 Hz), 6.16(s, 1H, C_1-H), 6.98(d, 1H, C_3-H, *J*=6.9 Hz), 7.30-7.70(m, 2H, Ar-H).

Antibacterial activity

Antibacterial activities of three of the synthesized compounds **3a-c** were screened for the *in vitro* growth

Table I — Antibacterial activities of compounds **3a-c**

Compd	Conc	Microorganism zone of inhibition (in mm)		
		S. typhii	*A. hydrophilla*	*E. coli*
3a	0.5%	-	1	2
	1%	1	4	3
	2%	4	8	7
3b	0.5%	1	2	2
	1%	5	6	5
	2%	9	10	8
3c	0.5%	2	4	5
	1%	6	7	9
	2%	13	10	15
Streptomycin (standard)	0.5%	6	5	4
	1%	9	8	7
	2%	15	13	12

[a] Values of the mean of three replicates; - no inhibition

inhibitory activity against *Aeromonas hydrophilla, Escherichia coli* and *Salmonella typhi* by the disc diffusion method[12]. The bacteria were cultured in nutrient agar medium and used as inoculum for this study. Bacterial cells were swabbed onto nutrient agar medium [prepared from NaCl (5.0 g), peptone (5.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), agar (20.0 g) in 100 mL distilled water, *p*H = 7.5 ± (0.2)] in petri plates. The compounds to be tested were dissolved in chloroform to a final concentration of 0.5, 1 and 2% and soaked in filter paper discs of 5 mm diameter and 1 mm thickness. These discs were placed on the already seeded plates and incubated at 35 ± 2°C for 24 hr. The diameter (mm) of the inhibition zone around each disc was measured after 24 hr and the results are listed in **Table I**. Streptomycin was used as standard.

All the compounds exhibited moderate activity against *Aeromonas hydrophilla* and *Salmonella typhi*. According to the observation, the toxicity increases with the increase in concentration of the test solution containing the new compounds. Although all the compounds are active, they did not reach the effectiveness of the conventional bacteriostatic streptomycin at lower concentration levels. Interestingly, the compound **3c** shows better activity than the standard in case of the microorganism *E. coli*. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or diffusion in ribosomes of microbial cells.

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